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*Published in:*  
Diabetes Research and Clinical Practice

*DOI:*  
[10.1016/j.diabres.2017.05.004](https://doi.org/10.1016/j.diabres.2017.05.004)

*Publication date:*  
2017

*Document version*  
Publisher's PDF, also known as Version of record

*Document license:*  
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*Citation for published version (APA):*  
Khunti, K., Alsifri, S., Aronson, R., Cigrovski Berkovi, M., Enters-Weijnen, C., Forsén, T., Galstyan, G., Geelhoed-Duijvestijn, P., Goldfracht, M., Gydesen, H., Kapur, R., Lalic, N., Ludvik, B., Moberg, E., Pedersen-Bjergaard, U., Ramachandran, A., & HAT Investigator Group (2017). Impact of hypoglycaemia on patient-reported outcomes from a global, 24-country study of 27,585 people with type 1 and insulin-treated type 2 diabetes. *Diabetes Research and Clinical Practice*, 130, 121-129. <https://doi.org/10.1016/j.diabres.2017.05.004>



Contents available at ScienceDirect

Diabetes Research  
and Clinical Practicejournal homepage: [www.elsevier.com/locate/diabres](http://www.elsevier.com/locate/diabres)International  
Diabetes  
Federation

# Impact of hypoglycaemia on patient-reported outcomes from a global, 24-country study of 27,585 people with type 1 and insulin-treated type 2 diabetes

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## ARTICLE INFO

### Article history:

Received 9 September 2016

Accepted 8 May 2017

Available online 12 May 2017

## ABSTRACT

**Aims:** Data on the impact of hypoglycaemia on patients' daily lives and diabetes self-management, particularly in developing countries, are lacking. The aim of this study was to assess fear of, and responses to, hypoglycaemia experienced by patients globally.

**Materials and methods:** This non-interventional, multicentre, 4-week prospective study using self-assessment questionnaires and patient diaries consisted of 27,585 patients,

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<http://dx.doi.org/10.1016/j.diabres.2017.05.004>

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**Keywords:**

HAT study

Hypoglycaemia

Observational

Insulin

Diabetes

Global

≥18 years, with type 1 diabetes ( $n = 8022$ ) or type 2 diabetes ( $n = 19,563$ ) treated with insulin for >12 months, at 2004 sites in 24 countries worldwide.

**Results:** Increased blood glucose monitoring (69.7%) and seeking medical assistance (62.0%) were the most common responses in the 4 weeks following hypoglycaemic events for patients with type 1 diabetes and type 2 diabetes, respectively. Approximately 44% of patients with type 1 diabetes or type 2 diabetes increased calorie intake in response to a hypoglycaemic episode. Following hypoglycaemia, 3.9% (type 1 diabetes) and 6.2% (type 2 diabetes) of patients took leave from work or study. Regional differences in fear of, and responses to, hypoglycaemia were evident – in particular, a lower level of hypoglycaemic fear and utilisation of healthcare resources in Northern Europe and Canada.

**Conclusions:** Hypoglycaemia has a major impact on patients and their behaviour. These global data for the first time reveal regional variations in response to hypoglycaemia and highlight the importance of patient education and management strategies.

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## 1. Introduction

Tight glycaemic control achieved through intensive insulin regimens has been shown to reduce the risk of long-term complications of diabetes and is often the goal of treatment for both type 1 and type 2 diabetes [1–4]. However, insulin therapy, and particularly intensive insulin therapy, is associated with an increased risk of hypoglycaemia [1–3]. Hypoglycaemia, in addition to morbidity and mortality, is associated with a reduction in health-related quality of life, increased fear and anxiety, reduced productivity and increased healthcare costs through increased utilisation of healthcare resources and blood glucose monitoring [5–8]. As a result, patients may take compensatory actions in order to avoid hypoglycaemia, such as reducing their insulin dose, reducing exercise levels or increasing their calorie intake [9,10], which can lead to poor glycaemic control.

Currently, the majority of data on the prevalence of hypoglycaemia and its consequences come from industrialised Western countries [1,7,9–13], with multinational studies focusing on economies with advanced healthcare systems. Estimates of the frequency of hypoglycaemia are 3.5–7.2 events/month (42–91 events per patient-year [PPY]) for type 1 diabetes [6,8,10,14] and 0.8–4.0 events/month (20.3–44.4 events PPY) for type 2 diabetes [6,8,10,14–17], and rates of hypoglycaemia increase with duration of disease and duration of insulin treatment [18]. Increasing frequency of non-severe hypoglycaemic events has been reported to lead to an increased risk of severe hypoglycaemic events [19,20]. Severe hypoglycaemia, defined by the American Diabetes Association (ADA) as requiring third-party assistance [21], accounts for significant medical expenditure due to hospitalisation [22–24] and a lower health-related quality of life [9], as well as increased mortality risks [11,12]. It is not surprising that patients respond to hypoglycaemia by taking compensatory actions to avoid future occurrences [7].

Until now, the impact of hypoglycaemia on patient behaviour has not been ascertained on a truly global level due to a requirement for systematic data capture, involving a large number of patients from different countries. Comparing potential country-specific differences based on current data

remains difficult due to differences between individual study designs.

In this study, we report on patient fear of, and responses to, hypoglycaemia from the Hypoglycaemia Assessment Tool (HAT) study – a global, 4-week prospective study of hypoglycaemia in clinical practice.

## 2. Research design and methods

### 2.1. Study design

This study was a non-interventional, multicentre, 4-week prospective-cohort survey of hypoglycaemic events conducted across 2004 sites in 24 countries (Argentina, Austria, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Finland, Germany, Hungary, India, Israel, Lebanon, Malaysia, Mexico, The Netherlands, Poland, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, and Sweden). The study was conducted from 2012 to 2013 in a staggered fashion (start times varied by country). The study protocol and assessments were conducted in accordance with the Declaration of Helsinki (2004) and the International Conference on Harmonization Guidelines for Good Clinical Practice (1996), and approved by country-specific regulatory agencies.

### 2.2. Study population

Consecutive eligible patients were enrolled during a routine scheduled clinical consultation with their healthcare provider. Eligible patients were ≥18 years of age at the time of enrolment, with type 1 diabetes or type 2 diabetes treated with insulin for >12 months. Exclusion criteria included non-ambulatory patients, illiterate patients or patients otherwise unable to complete a written survey.

### 2.3. Study objectives

The primary endpoint was the proportion of patients experiencing at least one hypoglycaemic event during the 4-week observational period (detailed methodology and results in Khunti et al. [25]). This manuscript reports on patient knowl-

edge and definitions of hypoglycaemia, fear of hypoglycaemia, patient actions as a result of a hypoglycaemic episode, and the impact of hypoglycaemia on work/study for patients currently enrolled in education or in part- or full-time employment.

#### 2.4. Assessments

This combined cross-sectional cohort study comprised a two-part self-assessment questionnaire (SAQ). Part 1 was used to record baseline demographic and treatment information, evaluate knowledge and perceptions of hypoglycaemia as well as the history of severe hypoglycaemia over the past 6 months and symptomatic hypoglycaemia over the past 4 weeks. Fear of hypoglycaemia was reported on a 10-point scale, with 0 as 'not afraid at all' and 10 as 'absolutely terrified'. Part 2 evaluated the history of both severe and symptomatic hypoglycaemia over the 4 weeks following baseline study entry, and the effect of hypoglycaemia on patient behaviour and productivity during this time frame. To assist recall in Part 2 of the SAQ, patients were provided with a diary to summarise their experience of hypoglycaemia at home and to help track them over the 4-week period. All study materials were translated into local languages, and data obtained were translated back into English for analysis. In the current manuscript, we report the impact on patients and changes in their behaviour and activity in response to hypoglycaemic episodes.

#### 2.5. Hypoglycaemia classification

Categories of hypoglycaemia recorded in the questionnaire and patient diary included non-severe hypoglycaemia, defined as an event based on either symptoms or self-monitored blood glucose <56 mg/dL (3.1 mmol/L), and managed by the patient alone; severe hypoglycaemia, defined, based on the ADA definition, as any hypoglycaemic event requiring assistance of another person to administer carbohydrate, glucagon or other resuscitative actions actively [21]; and nocturnal hypoglycaemia, any event occurring between midnight and 06.00 h. A combined measure of any hypoglycaemia, based on the sum of all individual hypoglycaemic events of any category, was calculated based on questionnaire entries. If a patient recorded more hypoglycaemic events using the patient diary than the Part 2 SAQ, the patient diary value was used to calculate the incidence of hypoglycaemia in the 4 weeks after baseline to compensate for potential underestimates due to recall bias.

#### 2.6. Statistical analysis

The proportion of patients who knew what hypoglycaemia was before they read the definition provided in the Part 1 SAQ (see Description of hypoglycaemia in the introduction to Part 1 SAQ in [supplementary material](#)) was summarised by diabetes type. Hypoglycaemic fear was summarised overall or by whether or not patients had experienced severe hypoglycaemia in the 6 months before baseline, and by diabetes type.

Pre-planned patient outcomes to assess the impact of hypoglycaemic events included consultation with a health-

care provider, requirement of medical assistance, increase in calorie intake, avoidance of physical exercise, reduction of insulin doses, skipping of insulin injections, and increased blood glucose monitoring. Additional outcome measures included sick leave and time lost from work or studies.

Summary statistics (n, mean, SD, lower quartile, median, upper quartile, minimum, maximum, and the number missing) were calculated.

### 3. Results

#### 3.1. Patient characteristics

A total of 27,585 patients (8022 type 1 diabetes; 19,563 type 2 diabetes) were enrolled, and completed Part 1 of the SAQ. Of these, 25,505 patients (7070 [88.1%] type 1 diabetes; 18,435 [94.2%] type 2 diabetes) completed Part 2 and 23,627 patients (6822 [85.0%] type 1 diabetes; 16,805 [85.9%] type 2 diabetes) completed the patient diary. Baseline disposition is summarised in [Table 1](#). Patients' baseline characteristics by region for type 1 diabetes and type 2 diabetes are shown in Tables S1 and S2, respectively.

#### 3.2. Patient beliefs about the nature of hypoglycaemia

A total of 96.8% (n = 7711) of patients with type 1 diabetes and 85.6% (n = 16,577) of patients with type 2 diabetes were able to define hypoglycaemia before reading the definition provided. In terms of their prior personal definition of hypoglycaemia, 49.1% (n = 3758) of patients with type 1 diabetes and 42.3% (n = 6231) of patients with type 2 diabetes incorporated both symptoms and blood glucose measurements ([Table 1](#)).

#### 3.3. Rates of hypoglycaemia

Estimated annual rates of any hypoglycaemia in the prospective period were 73.3 events PPY (95% CI 72.6–74.0) and 19.3 events PPY (95% CI 19.1–19.6) for patients with type 1 diabetes and type 2 diabetes, respectively (detailed results in Khunti et al. [25]).

Regional overall hypoglycaemia rates for type 1 diabetes were 91.6 events PPY (95% CI 90.0–93.2) for Northern Europe/Canada, 66.9 events PPY (95% CI 65.8–67.9) for Eastern Europe, 93.9 events PPY (95% CI 90.6–97.3) for Latin America, 66.2 events PPY (95% CI 64.4–68.1) for the Middle East, 69.2 events PPY (95% CI 66.8–71.6) for Russia, and 17.5 events PPY (95% CI 15.5–19.6) for SE Asia.

Regional overall hypoglycaemia rates for type 2 diabetes were 18.1 events PPY (95% CI 17.6–18.7) for Northern Europe/Canada, 23.7 events PPY (95% CI 23.2–24.1) for Eastern Europe, 19.7 events PPY (95% CI 18.9–20.6) for Latin America, 15.4 events PPY (95% CI 14.9–15.9) for the Middle East, 28.1 events PPY (95% CI 26.8–29.6) for Russia, and 14.6 events PPY (95% CI 14.2–15.1) for SE Asia.

#### 3.4. Fear of hypoglycaemia

At baseline, mean  $\pm$  SD scores for self-rated fear of hypoglycaemia were  $4.7 \pm 3.0$  for patients with type 1 diabetes and

**Table 1 – Characteristics of the study population.**

Characteristic	Type 1 diabetes (n = 8022)	Type 2 diabetes (n = 19,563)
Sex male/female, %	48/52	53/47
Mean age, years (SD)	42.1 (15.1)	60.8 (10.9)
Median (upper quartile, lower quartile)	40 (53, 30)	61 (68, 54)
Duration of diabetes, years (SD)	17.6 (12.0)	13.7 (8.2)
Median (upper quartile, lower quartile)	15 (24, 8)	12 (18, 8)
HbA <sub>1c</sub> , % (SD)	7.9 (1.5)	8.0 (1.5)
HbA <sub>1c</sub> , mmol/mol (SD)	62.8 (16.2)	64.2 (16.3)
Median (upper quartile, lower quartile)	61.0 (70.5, 51.9)	61.8 (72.7, 53.0)
Checks blood sugar levels, n (%)		
Yes	7888 (98.6)	17,858 (91.6)
No	110 (1.4)	1635 (8.4)
Experienced hypoglycaemia, n (%)		
Yes	7759 (97.4)	15,167 (78.3)
No	159 (2.0)	3272 (16.9)
Not sure	49 (0.6)	940 (4.9)
Defined hypoglycaemia on basis of, n (%)		
Symptoms only	2051 (26.8)	5251 (35.6)
Blood glucose measurement only	300 (3.9)	1066 (7.2)
Either	1545 (20.2)	2195 (14.9)
Both	3758 (49.1)	6231 (42.3)

\* Calculated, not measured. SD, standard deviation.

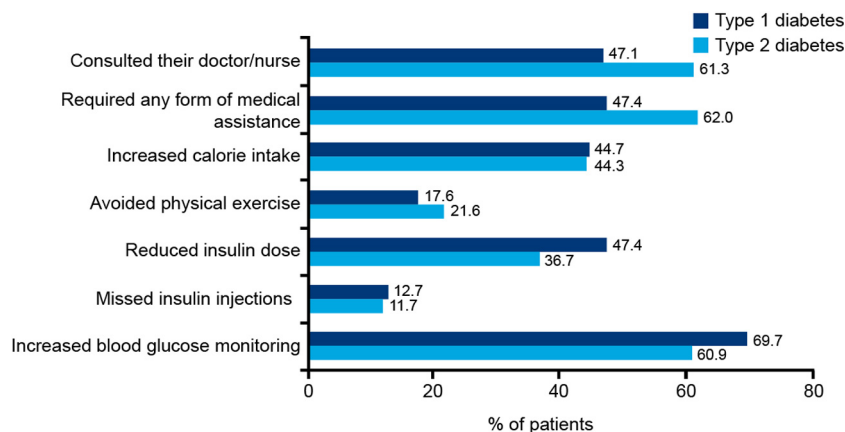
4.4 ± 3.1 for patients with type 2 diabetes. Overall, 7.4% and 6.7% of patients with type 1 diabetes and type 2 diabetes, respectively, reported a level of fear of hypoglycaemia as 'absolutely terrified'. The proportion of patients (type 1 and 2 diabetes combined) with no history of severe hypoglycaemia reporting 'not afraid at all' was 15.8%, whilst 5.6% were 'absolutely terrified'. Among patients (type 1 and 2 diabetes combined) with a history of severe hypoglycaemia, the proportion who reported their level of fear as 'not afraid at all' was 6.2%, whilst 12.2% were 'absolutely terrified'.

Regional differences in patients' fear of hypoglycaemia were evident (Table S3), with patients in Northern Europe and Canada having the lowest mean scores both for patients with type 1 diabetes and those with type 2 diabetes (3.9 and 2.9, respectively) and patients in the Middle East having the highest mean scores (5.5 for type 1 diabetes and 5.4 for type 2 diabetes).

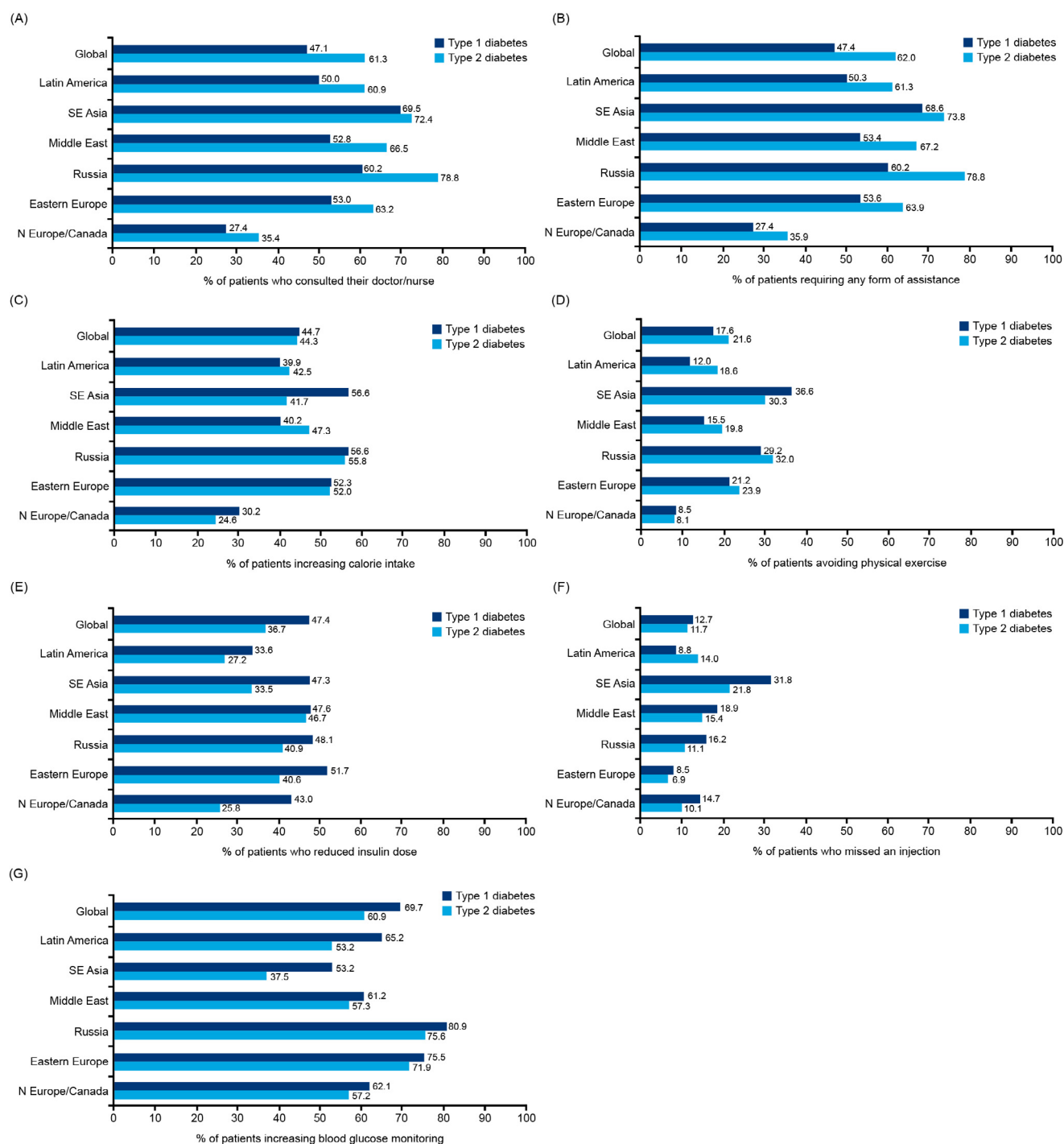
### 3.5. Patient actions

Patients' actions in response to experiencing hypoglycaemia varied between regions (Figs. 1 and 2). Regional trends with regard to consulting their doctor/nurse, and/or requiring medical assistance (Fig. 2A and B) for both, approximately half to two-thirds of patients responded to hypoglycaemia in these ways in all regions, except Northern Europe/Canada, where these responses were substantially less common (one-third of patients or fewer). In all regions, patients with type 2 diabetes were more likely to consult their doctor/nurse or require medical assistance than patients with type 1 diabetes (Fig. 2A and B).

The proportion of patients who avoided physical exercise in response to hypoglycaemia also varied between regions, with approximately one-third doing so in Russia and SE Asia compared with <10% in Northern Europe/Canada (Fig. 2D).

**Fig. 1 – Patient actions resulting from hypoglycaemia in the 4 weeks following baseline.**





**Fig. 2 – Regional breakdowns for patients who A: consulted their doctor/nurse, B: required any form of medical assistance, C: increased calorie intake, D: avoided physical exercise, E: reduced insulin dose, F: missed an injection, and G: increased blood glucose monitoring in response to hypoglycaemia during the prospective period.**

Reducing insulin dose was a common response to hypoglycaemia in all regions, ranging from 33.6% to 51.7% in patients with type 1 diabetes and from 25.8% to 46.7% in patients with type 2 diabetes (Fig. 2E). In all regions, a greater proportion of patients with type 1 diabetes reduced their insulin dose in response to a hypoglycaemic event compared with patients with type 2 diabetes. However, the extent of this difference varied between regions, with patients with type 2

diabetes in the Middle East almost as likely to reduce insulin dose as those with type 1 diabetes (46.7% vs. 47.6%, respectively), whereas in Northern Europe/Canada, patients with type 2 diabetes were considerably less likely to reduce insulin dose than patients with type 1 diabetes (25.8% vs. 43.0%, respectively).

There was considerable variation between the regions in the proportion of patients who missed an injection in

response to hypoglycaemia (8.5–31.8% for patients with type 1 diabetes; 6.9–21.8% for patients with type 2 diabetes) (Fig. 2F). This response was most common in SE Asia. In five out of six regions, patients with type 1 diabetes were more likely to miss an injection than those with type 2 diabetes; Latin America was the exception.

Finally, high proportions of patients across all regions increased blood glucose monitoring following hypoglycaemia (Fig. 2G), and this response was more common in patients with type 1 diabetes (69.7% globally) than with type 2 diabetes (60.9% globally). The duration of additional monitoring lasted for  $2.7 \pm 4.3$  days and  $1.8 \pm 3.2$  days for type 1 and type 2 diabetes, respectively.

### 3.6. Impact of hypoglycaemia on the medical system, and on work and study

Globally, 2.1% of patients with type 1 diabetes and 3.4% of patients with type 2 diabetes had a hypoglycaemic event requiring hospital admission in the 4 weeks following baseline, whereas 3.8% and 6.8%, respectively, attended additional clinic appointments as a result of hypoglycaemia. Additional telephone contacts to medical personnel as a result of hypoglycaemia were reported by 8.8% of patients with type 1 diabetes and 16.0% of patients with type 2 diabetes. Of those patients who took leave from work or study as a result of hypoglycaemia, patients with type 1 diabetes reported taking a mean 2.0 days off work or study in the 1-month prospective period, and patients with type 2 diabetes reported taking a mean 1.8 days off work or study due to hypoglycaemia in the 1-month prospective period (Tables S4 and S5).

## 4. Discussion

The HAT real-world study, the largest prospective observational study of hypoglycaemia to date, has demonstrated global hypoglycaemia rates higher than previously reported from studies focused on Western countries [18,20,26], with the highest rates in patients with type 1 diabetes in Northern Europe and Canada, and Latin America, and the highest rates in patients with type 2 diabetes in Russia and Eastern Europe (these data are discussed in more detail in Khunti et al. [25]). In addition, the results show that hypoglycaemia influenced patient behaviour that could affect both glycaemic control and the cost burden to healthcare systems, with approximately half of all patients saying they consulted a doctor or nurse and almost half of patients with type 1 diabetes reduced insulin dose as a result of hypoglycaemia. A sizeable proportion (>40%) of patients who experienced a hypoglycaemic event in the prospective period said that they consulted a doctor/nurse, required medical assistance, increased calorie intake or increased blood glucose monitoring. There were notable differences in patient responses across geographic regions. Patients with a history of severe hypoglycaemia within the previous 6 months were more likely to report greater fear of hypoglycaemia than those without a history of severe hypoglycaemia. Overall, 7.4% and 6.7% of patients with type 1 diabetes and type 2 diabetes, respectively, reported their level of fear of hypoglycaemia as 'absolutely terrified'. This finding is of note given that the study

comprised a large multinational population of more than 25,000 patients. Overall, an increase in fear of hypoglycaemia was seen for patients with a history of severe hypoglycaemia compared with those without. Fear of hypoglycaemia also varied between regions, being generally higher in regions outside of Europe and Canada, but these were not necessarily the regions with the highest rates of hypoglycaemia [25]).

Limitations of this study include its observational nature and short prospective duration. More importantly, such a trial design allowed for a large, multinational patient population to complete the study and offered the possibility to examine country-specific differences in a global population. The use of diary-based data in the prospective period may have increased the reliability of data on incidence and prevalence of hypoglycaemia and patient actions, although taking the highest of the patient-reported values for hypoglycaemia incidence could potentially overestimate hypoglycaemia rates in this study. Furthermore, the use of self-reported patient questionnaires and diaries could introduce bias into the population, depending on willingness to participate and local literacy rates.

Similar to previous self-reporting studies, patients in the HAT study were permitted to record hypoglycaemia by either symptoms or blood glucose testing alone, or in combination. This is both a strength and a limitation of the study. Including episodes of hypoglycaemia on the basis of symptoms alone captures events in which patients forgot or neglected to test blood glucose, were unaware of the blood glucose concentration cut-off for hypoglycaemia, or were unable to test due to a lack of testing devices/materials. However, the subjective nature of patients self-defining hypoglycaemia on the basis of symptoms alone introduces the potential for confounding due to differences in the levels of patient education regarding hypoglycaemia cut-offs. Similarly, differences in healthcare provision and local economic conditions could affect access to patient education and blood glucose monitoring materials, which in turn could affect recording of hypoglycaemic episodes. A high-level of education regarding hypoglycaemia could be defined as an understanding that hypoglycaemia can occur independently for both blood glucose cut-offs and symptoms, and this may not be the case for a large proportion of the study population. However, these factors, patient education and healthcare provision, are also highly likely to affect the incidence of hypoglycaemia.

The changes in patient behaviour in response to hypoglycaemia reported here have been previously observed in response to both nocturnal [6] and overall non-severe hypoglycaemia [7,13,27]. Greater fear of hypoglycaemia reported by patients with a history of severe hypoglycaemia is consistent with previous reports [28]. However, this global study has identified considerable regional differences in patients' responses to hypoglycaemia, suggesting that the management and importance of hypoglycaemia differs markedly in different parts of the world, and underlining the importance of gathering regional data in order to individualise interventions and educational measures.

The patient actions in response to hypoglycaemia reported here (consulting a doctor/nurse, requiring medical assistance, increasing calorie intake or increasing blood glucose monitoring) could result in increased costs for the patient and/or the

healthcare system, or hinder achievement of good glycaemic control.

Patients in SE Asia were least likely to increase blood glucose monitoring in response to hypoglycaemia, which could reflect the local healthcare systems and cost burden of blood glucose testing for patients. In Northern Europe and Canada, where patients had the lowest fear of hypoglycaemia, despite higher actual rates of hypoglycaemia, substantially fewer patients consulted a doctor or nurse, or required medical assistance as a result of hypoglycaemia, which may reflect a high level of patient education and ability to self-manage their diabetes. In other countries, an underlying reason may be a reluctance to go to the doctor due to the costs for the patient associated with the clinic visit. Interestingly, the regions that had the greatest numbers of patients missing insulin injections, avoiding physical exercise or increasing calorie intake in response to hypoglycaemia (activities that may adversely impact treatment) and those regions with the greatest number of patients consulting a doctor or nurse, were also those with the greatest fear of hypoglycaemia. Fear of hypoglycaemia led patients to take actions that may have hampered glycaemic control, suggesting that a substantial proportion of patients with diabetes worldwide could be prevented from achieving individual treatment goals [9,29]. However, caution should be used in interpreting these results, as they could be due to a variety of factors such as culture, genetics, diet, lifestyle, available treatments, healthcare and reimbursement systems, and access to relevant information and support. Patient education is important to prevent hypoglycaemia adequately and to ensure that actions in response to hypoglycaemia do not adversely impact treatment, but instead result in improved self-management and appropriate use of available support. Self-management programmes have been shown to reduce hypoglycaemia in trials of intensive treatment, while also achieving tighter glycaemic control [30–32].

Although this study identified considerable regional differences in patient response to hypoglycaemia that may affect the cost and effectiveness of treatment, the underlying reasons remain to be determined. Further studies and analyses are required to investigate the contributions of cultural differences and differences in healthcare approaches. Understanding the true frequency of hypoglycaemia and its impact on patient behaviour in different parts of the world will be an important part of tailoring insulin treatment for patients with diabetes.

### Conflict of interest

K.K. has acted as a consultant, advisory board member, and speaker for and has received research grants from Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Sanofi, Boehringer Ingelheim, and Roche. S.A. has no conflicts of interest to disclose. R.A. has provided research support, acted as a consultant and advisory board member, and has received research grants from Novo Nordisk, Janssen, Sanofi, Medtronic, Bristol-Myers Squibb, AstraZeneca, Takeda, Becton Dickinson, Merck Sharp & Dohme, Boehringer Ingelheim, Regeneron, Eli Lilly, Abbot, Quintiles,

ICON, Medpace, and GlaxoSmithKline. M.C.B. has acted as a board member for Novo Nordisk and Novartis, and speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, AstraZeneca, Sanofi, Boehringer Ingelheim, and Novartis. C.E.-W. has received unrestricted educational grants from Novo Nordisk and Pfizer. T.F. has no conflicts of interest to disclose. G.G. has acted on advisory panels and as a board member and speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, AstraZeneca, Sanofi, Novartis, and Takeda. P.G.-D. has acted as a speaker for and received research grants from Novo Nordisk. M.G. has no relevant conflicts of interest to disclose. H.G. and R.K. are employees of Novo Nordisk. N.L. has no conflicts of interest to disclose. B.L. has acted as an advisory board member and speaker for Amgen, Allergan, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Serono KGaA, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi, and Servier. E.M. has acted as a speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Sanofi, and Boehringer Ingelheim. U.P.-B. has acted as a consultant, advisory board member, and speaker for and has received research grants from Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Sanofi, Boehringer Ingelheim, and Roche. A.R. has acted as an advisory board member and speaker for AstraZeneca, Bristol-Myers Squibb, Novo Nordisk, and Sanofi and has received research grants from Novo Nordisk.

### Author contributions

K.K. designed the study and developed the protocol for this current ongoing research programme, drafted the manuscript and designed the analysis plan.

S.A. designed and performed the research, and contributed to the manuscript.

R.A. performed the research, carried out data interpretation and wrote the manuscript.

M.C.B. performed the research, carried out data analysis and wrote the manuscript.

C.E.-W. contributed to writing the manuscript.

T.F. designed and performed the research, and contributed to the manuscript.

G.G. carried out data analysis.

P.G.-D. designed and performed the research, carried out data interpretation and wrote the manuscript.

M.G. performed the research, carried out data analysis and wrote the manuscript.

H.G. designed the study and carried out data analysis.

R.K. designed the study, analysed and interpreted the data, and wrote the manuscript.

N.L. performed the research.

B.L. designed the study, carried out data analysis and wrote the manuscript.

E.M. designed and performed the research and wrote the manuscript.

U.P.-B. performed the research, carried out data analysis and wrote the manuscript.

A.R. carried out data analysis and reviewed the manuscript.



## Acknowledgments

Statistical analysis was performed by Parexel. The authors acknowledge medical writing support provided by Water-meadow Medical and apothecom scopemedical, both funded by Novo Nordisk A/S, Denmark.

K.K. is supported by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CIAHRC – EM), the Leicester Clinical Trials Unit and the NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester, UK.

All authors had input into the data interpretation and preparation of the final manuscript for publication, and met the ICMJE criteria for authorship. The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabres.2017.05.004>.

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